REMARKS

Claims 32, 33, 49-50 and 78 have been amended. Claims 1-31, 34-35, 38-40, 58-73, 76 were previously canceled without prejudice or disclaimer. Subsequent to the entry of the present amendment, claims 32-33, 36-37, 41-57, 74-75 and 77-78 are pending and at issue. These amendments and additions add no new matter as the amendments are fully supported by the specification and original claims.

I. Amendment to the Specification and Claims

The paragraphs following the "Brief Description of the Drawings" have been amended to include sequence identification numbers. No new matter has been added, as the sequence identification numbers are found in the Sequence Listing. Filed June 8, 2006.

Claims 32, 33, 49-50 and 78 have been amended.

Claims 32 and 78 have been amended, in part, per the suggestion of the Office Action. The claims have also been amended to clearly recite a method of identifying a test agent which affects isopeptidase activity by measuring the deconjugation of the modifier protein from the target protein in the presence or absence of the a 26S proteasome inhibitor (claim 32) or a metalloprotease inhibitor (claim 78). Amendment to claim 32 is supported in the application and original claims, e.g. paragraphs [0050]-[0051], [0060]-[0062], [0068] and [0075] and original claims 49-50. Amendment to claim 78 is supported in the application in Example 3 , paragraph [0090].

Claim 33 has been amended to improve its form and per the suggestion of the Office Action.

Claims 49 and 50 have been amended because the subject matter of "26S proteasome" inhibitor has been incorporated into claim 32.

The amendments to the claims do not add new matter.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

A. Rejection of claims 32-33 and 78

Claims 32-33 and 78 and claims 36-37, 41-57, 74-75 and 77 depending therefrom are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection as it applies to the pending claims.

According to the Office Action (page 3):

> Claims 32-33 and 78 recite the phrase "as set forth in". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner if the recited polypeptide/peptide has the amino acid sequence of SEQ ID NO:2, 7, 23 and 24 or is a representative member of a genus.
>
> Examiner suggests amending the phrase as "the Rpn11 polypeptide comprising the amino acid sequence of SEQ ID NO:23 or 24" (claim 32), "the amino acid sequence... of SEQ ID NO:2" (claim 33) and "AMSH polypeptide comprises the amino acid sequence of SEQ ID NO:7 (claim 78) to clearly indicate that the polypeptide/peptide recited in the method has the amino acid sequence of SEQ ID NO:2, 7, 23 or 24.

Claims 32, 33 and 78, and dependent claims therefrom, have been amended per the suggestion of the Office Action.

Accordingly, withdrawal of rejection of claims 32-33 and 78, and dependent claims therefrom, under 35 U.S.C. §112, second paragraph is respectfully requested.

B. Rejection of claim 32 and 78

Claims 32 and 78 and claims 33, 36-37, 41-57, 74-75 and 77 depending therefrom are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection as it applies to the pending claims.

According to the Office Action (emphasis added; page 4):

> Claims 32 and 78 recite the phrase "determining the isopeptidase activity of the test agent by measuring deconjugation of the modifier protein from the target protein". The metes and bounds of the phrase in the context of the above claims are not clear to the Examiner. It is not clear to the Examiner as to what applicants mean by "determining the isopeptidase activity of the test agent". Furthermore, it is also not clear as to how those skilled in the art can conclude that the agent identified by the above method modulates isopeptidase activity of Rpn11 or AMSH. It is not clear to the Examiner as to how applicants or those skilled in the art would recognize that said agent being tested is indeed specifically affecting isopeptidase activity of Rpn11 or AMSH and not directly causing the cleavage of the modifier protein from the target protein without affecting the isopeptidase.
>
> ...it is not clear to the Examiner as to how applicants or those skilled in the art would recognize that said agent being tested is indeed specifically affecting isopeptidase activity of Rpn11 or AMSH and <u>not directly causing the cleavage of the modifier protein from the target protein without affecting the isopeptidase</u>.
>
> Therefore, the *method lacks essential step(s)*...

Claim 32, and dependent claims therefrom, have been amended to recite a method of identifying a test agent which affects Rpn11 isopeptidase activity by measuring the deconjugation of the modifier protein from the target protein in the presence or absence of the a 26S proteasome inhibitor. Use of a 26S proteasome inhibitor is described throughout the application and original claims, e.g. paragraphs [0050]-[0051], [0060]-[0062], [0068] and [0075] and original claims 49-50.

Claim 78 has been amended to recite a method of identifying a test agent which affects AMSH isopeptidase activity by measuring the deconjugation of the modifier protein from the

target protein in the presence or absence of a metalloprotease inhibitor. Use of a metalloprotease inhibitor is supported in the application in Example 3 , paragraph [0090].

The amendments to claims 32 and 78, and dependent claims therefrom, particularly point out that the isopeptidase activity of Rpn11 or AMSH are affected by either a 26S proteasome (claim 32) or metalloprotease inhibitor (claim 78). Example 1 describes that in the presence of epoxomicin, ubiquinated Sic1 was completed degraded by the 26S proteasome (paragraph [0061] and [0068]). Example 3 describes that metalloprotease inhibitors will inhibit the active site of AMSH proteins, thereby inhibiting the ability of the AMSH proteins to deconjugate a modifier protein from a target protein.

Thus, based on the foregoing, the claimed methods do not lack an essential step as the steps that are required and which Applicants believe is the claimed invention, which invention is supported in the application as filed.

Accordingly, withdrawal of rejection of claim 32 and 78 under 35 U.S.C. §112, second paragraph is respectfully requested.

CONCLUSION

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

No fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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